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Review article

Acute kidney injury in the elderly: Only the tip of the iceberg

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ABSTRACT

The incidence of acute kidney injury (AKI) is rising in individuals of all ages; however, elderly patients (older than 65 years) are particularly susceptible to the development of AKI due to the structural and functional deterioration of the kidneys associated with the aging process, a decreased renal reserve, the presence of comorbidities, and the reduced ability to recover. Older patients with AKI carry an elevated risk of both short-term and long-term mortality, and survivors are often left with chronic kidney disease (CKD) that eventually progresses to end-stage renal disease (ESRD). Additionally, older patients with AKI suffer from an impaired quality of life and decreased functional status, both of which contribute to adverse outcomes. Maintaining adequate hydration and avoiding nephrotoxic agents are helpful in warding off AKI in elderly individuals. No proven treatment measures exist for AKI in elderly individuals except supportive therapy. A thorough understanding of the pathogenesis, etiology, clinical courses, complications, and prognosis of AKI in the elderly population is vital to preemptively reduce the incidence of AKI and hopefully create a better outcome.

1. Introduction

Acute kidney injury (AKI), previously termed acute renal failure (ARF), has attracted increasing attention in recent years as a result of its rising incidence and its devastating effect on patients.[1,2] Annually, AKI occurs in approximately 0.3–0.5% of community-dwelling adults, 5–10% of all hospitalized patients, and 25–70% of critically ill patients.[2–7] Patients in whom AKI is diagnosed during hospital admission have a threefold to sixfold higher risk for hospital death and a threefold higher risk for prolonged hospital stay.[2,8] Consequently, AKI constitutes a public health emergency that must be addressed.

Aging is associated with a decline in organ function and the emergence of chronic diseases as a result of the accumulated damages to these vulnerable organ systems.[9] An analysis of Medicare beneficiaries in the United States showed that the rate of AKI increases stepwise from 13.6 episodes (66–69 years) to 18.1 episodes (70–74 years) to 24.9 episodes (75–79 years) to 34.2 episodes (80–84 years) to 46.9 episodes (85 years and older) per 1000 patient-years, respectively.[10,11] This trend holds true for both dialysis-requiring and nondialysis-requiring AKI.[12] However, few studies specifically address AKI in the elderly population, despite the continuous growth of this population and their higher chances of experiencing AKI.[13,14] In this review, we provide a brief description regarding the clinical features, classification schemes, disease courses, and outcomes of AKI in the elderly population, with a special focus on the inherent differences between the elderly and the general population.

2. Incidence of AKI in the elderly

The incidence of AKI in the elderly has been steadily growing across racial and geographic areas, especially among men.[14] Although this trend can be partially explained by the improved sensitivity of diagnostic methods and newer biomarkers, it is more likely that a true increase in the number of AKI patients exists, thus creating a silent epidemic. Few studies exist regarding the incidence of AKI among elderly patients in Taiwan. Our group estimated the incidence of AKI [defined as maximal serum creatinine (sCr) during admission divided by baseline sCr level, ratio $\geq$1.5] at 52.8% of all the elderly patients receiving major surgery associated with intensive care unit (ICU) admissions.[15] In China, a single-center study reported the incidence of AKI at 14.8% among patients >80 years admitted to the hospital; most of these cases were caused by sepsis.[16] The wide variation in the incidence of AKI stems directly from the population being studied, the circumstances leading to AKI, and the definition of AKI used during the studies.

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3. Pathophysiologic changes in the kidney of the elderly

3.1. Normal aging kidney

Kidney function declines after the biologic ages of 30–40 years.[17] The classic works of Davies and Shock[18] in the 1950s established the notion of functional renal aging, with 50% of renal function still remaining at age 90 years. This decline in renal function was considered purely physiologic and did not account for any comorbid conditions.[19,20] The origin of renal senescence has been associated with the renal vascular response to various mediators (e.g., acetylcholine and angiotensin), but efforts dedicated to reverse such effects have been mostly futile.[21,22]

Anatomically, the aging kidney can be discussed in microscopic and macroscopic terms. Microscopically, the functional unit (i.e., nephron) is often accompanied by glomerulosclerosis, with vascular tuft collapse, thickening of the glomerular basement membrane, and intracapsular fibrosis.[23–25] Tubular atrophy and interstitial fibrosis with collagen deposition also progress with aging.[25] Moreover, arteriosclerosis, medial hypertrophy, and arteriolar hyalinosis tend to accumulate with age, leading to glomerular ischemia and nephron degeneration.[24,25] The combination of the aforementioned histologic changes constitute the finding of nephrosclerosis, which can be quantified under light microscopy.[26] A cross-sectional study from the Mayo Clinic demonstrated that the percentage of nephrosclerosis increases in a stepwise fashion with aging (2.7% at 18–29 years; 16% at 30–39 years, 28% at 40–49 years; 44% at 50–59 years; 58% at 60–69 years, and 73% at 70–77 years).[25] However, anatomical changes do not necessarily correlate with changes in renal function. Other less frequently found phenomena include shrunken glomeruli, decreased glomerular density, and diverticuli.[27,28] Although renal weight decreases beyond 40–50 years of age,[29] kidney volume does not decrease in parallel fashion largely as a result of compensatory glomerular hypertrophy and/or an increase in sinus fat.[28] Abnormalities seen on ultrasound or computed tomography (such as distorted renal contours, surface lobulation, and markedly decreased size) are generally related to comorbidities and not the aging process.[30] Gross changes of the aging kidney mainly involve parenchymal calcifications, simple renal cysts, and focal narrowing of renal arteries[31]; however, none of these morphologic phenotypes readily imply a decline of renal function.

3.2. Effect of aging on the development of AKI

The kidney behaves differently as it ages. Experimental studies showed that older rats experience more severe kidney damage during ischemia and reperfusion maneuvers as a result of reduced antioxidant levels and higher oxidative stresses than do the kidneys of their younger counterparts.[32] Age also predisposes animals to other nephrotoxic injuries, such as from hemoglobin.[33] This exquisite susceptibility to exogenous and endogenous stimuli could be the result of structural and functional alterations during extreme aging.

4. Risk factors for AKI in the elderly

Multiple factors predispose the elderly to AKI. With advanced age, comorbidities including hypertension, diabetes mellitus, and heart failure can damage renal vasculature and compromise renal perfusion.[34] Comorbidities are often associated with the use of medications (such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) that can potentially increase the risk of AKI.[35] Nephrotoxins (such as contrast agents with iodine and nonsteroidal anti-inflammatory drugs) are also used with higher frequency in the elderly and predispose these patients to AKI.[36] Additionally, degeneration of other organs might necessitate various interventions or procedures that create occult insults to the already vulnerable kidneys.[37] Furthermore, preexisting chronic kidney disease [as defined according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines] in the elderly could precede the development of AKI.[38] The risk of sepsis is also higher in the elderly as a result of the decreased effectiveness of the immune system, which also predisposes the elderly to the development of AKI.[39]

Anatomical changes in the elderly are also responsible for their susceptibility to AKI. AKI arising from a postrenal origin (e.g., benign prostatic hyperplasia) occurs in 25% of elderly patients.[40] An increasing risk of pelvic cancer (e.g., bladder, colorectal, and prostate) with aging also contributes to a higher incidence of obstructive uropathy and subsequent AKI.[41] Glomerular changes, such as membranous glomerulopathy and amyloid depositions, are more common in the elderly.[42] These pathologic changes, along with proteinuria, also predispose the elderly to the development of subsequent renal injury.

5. Clinical features of AKI in the elderly

5.1. Etiology of AKI

Because the incidence of renal biopsy in the elderly is low, most of the etiologies for AKI in the elderly are based on clinical judgment, and the data are limited.[43] According to one report, ischemia (hypovolemia/hypotension) is responsible for half of the AKI cases, followed by surgery (33.3%), sepsis (10%), and nephrotoxins (3%).[44] Other larger studies suggested acute tubular necrosis as the most common cause of AKI in the elderly (39%), and prerenal conditions accounted for 30% of AKI.[41,45] Nonetheless, all reports identified prerenal or ischemic causes for the greatest proportion of AKI in the elderly.

5.2. Clinical features

No study currently addresses the key clinical differences between the elderly and younger patients with respect to the onset of AKI. Gong et al,[44] in a small-scale study, found no significant differences between the age groups with respect to sex, laboratory test results, proteinuria/hematuria, or disease severity scores [Acute Physiology and Chronic Health Evaluation (APACHE)], except for a longer hospital stay in the elderly group ($p = 0.038$). Several studies reported that aging diminishes the ability of the kidneys to recover after AKI occurs.[46,47] The putative mechanism might involve the age-dependent decline in specific tubular cells with regenerative potentials.[48] Elderly patients with AKI fare worse than their non-AKI counterparts during admission and carry a worse prognosis, with higher short-term and long-term mortality even after discharge from the index admissions.[49]

6. Diagnosis and classification of AKI in the elderly

Historically, the diagnosis of AKI (or ARF) was based on different criteria, depending on the percentage and the magnitude of the serum creatinine or changes in the urine volume over different intervals.[50] For clarification, we will summarize the information in the following paragraphs. The risk injury failure loss end-stage (RIFLE) classification system was established in 2004 by the Acute Dialysis Quality Initiatives (ADQI) consensus as a practical classification scheme for AKI[1] (Table 1). This classification unifies the threshold of changes in the biologic parameters (i.e., sCr and urine output) and limits the diagnostic window to 1 week. ADQI

Table 1
Risk injury failure loss end-stage (RIFLE) classification of acute kidney injury.

	sCr criteria	GFR criteria	Urine output criteria
Risk	sCr increase ≥1.5-fold	GFR decrease >25%	Urine < 0.5 mL/kg/h for 6 h
Injury	sCr increase ≥2-fold	GFR decrease >50%	Urine < 0.5 ml/kg/h for 12 h
Failure	(1) sCr increase ≥3-fold (2) sCr acute rise ≥0.5 mg/dL if baseline sCr ≥4 mg/dL	GFR decrease >75%	(1) Urine < 0.3 ml/kg/h for 24 h (2) Anuria for 12 h
Loss	Complete renal function loss for >4 wk		
End-stage	End-stage renal disease, defined as renal functional loss for >3 mo		

GFR = glomerular filtration rate (ml/min/1.73 m^2); sCr = serum creatinine (mg/dL).

proposed another classification system 3 years later, termed AKI network (AKIN). The diagnostic window was increased to 48 hours in order to enhance sensitivity[51] (Table 2). Both classification systems are useful in predicting the outcomes of critically ill patients, those with a wide spectrum of diseases, and those undergoing various surgeries/procedures.[52–57] Compared with non-AKI patients, RIFLE risk, injury, and failure classes of AKI are associated with a 2.4-, 4.1-, and 6.4-fold higher risk of adverse outcomes, respectively, in patients with AKI.[58]

Several biologic phenomena recognized in the elderly could contribute to the failure of the outcome-prediction model when we utilize these classification systems.[15] First, creatinine alone is never a good marker for estimating renal function.[59] Serum creatinine is frequently affected by the rate of creatinine production and many nonrenal issues, such as the overall nutrition status and the percentage of muscle mass (both of which are generally lower in the elderly).[60] Fluid overload or sepsis tend to develop more easily in older patients, which causes a disproportionately lower rise in sCr.[61,62] In addition to the falsely low sCr levels, the rate of sCr elevation in the elderly is also much slower than that of the general population, leading to an artificially late diagnosis of AKI.[63] Predictably, the use of sCr-based diagnosis and stratification methods, such as the RIFLE and AKIN schemes, will encounter limitations when applied to a geriatric population. We recently identified that age older than 76 years was associated with the failure of RIFLE to accurately predict the outcomes of geriatric AKI patients.[15]

Many researchers are now looking to other promising biomarkers for the diagnosis of AKI, with the hope of earlier detection and the institution of preemptive measures[59] (Table 3). Among these biomarkers, neutrophil gelatinase-associated lipocalin (NGAL) is the most well known. Plasma NGAL starts to elevate within 48–72 hours of cardiopulmonary bypass and other cardiac surgery-related AKI. Urinary NGAL elevation significantly predicts adverse outcomes in patients with AKI and sepsis, as well as in patients seen in the emergency department and in the ICU.[64,65] Levels of urinary liver-type fatty acid binding protein are also predictive for postoperative AKI in cardiac surgery patients.[66,67] Serum and urine interleukin-18 levels correlate fairly well with the development of postcardiopulmonary bypass AKI but are unreliable in the ICU or posttrauma settings.[68] Serum and urine cystatin C can be used to predict the development of AKI in postcardiac surgery patients and those who have undergone contrast-induced nephropathy. Urine kidney injury molecule-1 is utilized in postcardiac surgery cases.[69] Due to the wide variation in the definitions for AKI, clinical settings, study designs, and timing of the biomarkers, there is no current consensus about which biomarker should be used in which clinical scenarios. Furthermore, there are no current studies addressing the application of these novel biomarkers as risk predictors of AKI specifically in the elderly.

Diagnosis of AKI based on the International Classification of Disease (ICD) codes is controversial, as this method often underestimates the true incidence of AKI.[70,71] A recent study revealed that utilizing ICD-10 coding for capturing the diagnosis of AKI in the elderly could be highly specific (>95%) but not sensitive enough (37–62%).[72] This low sensitivity underscores the limitations of administrative databases in the studies of AKI, especially in geriatric cases.

7. Treatment strategies

The general principles of treating AKI in the elderly are similar to those of the other populations and involve treatment of life-threatening complications such as dyselectrolytemia, refractory metabolic acidosis, fluid overload (pulmonary edema), uremic bleeding, and uremic encephalopathy.[73] The elderly are more susceptible to fluid overload, and earlier interventions should be instituted to prevent complications.[61] The therapies delivered to these fragile elderly patients can potentially do more harm than good.[74] Judicious use of medication including dose adjustments for renal and liver dysfunction is vital for proper management of complications in elderly patients with AKI. Nutritional support in patients with AKI, particularly the elderly, is another underexplored area.

The initiation of renal replacement therapy (RRT) in AKI is a controversial issue, including early versus late initiation of RRT, high versus low RRT dosages, and methods for administration of RRT.[75] However, when it comes to the elderly, shared decision-making regarding life expectancy should be integrated into the

Table 2
Acute Kidney Injury Network classification of acute kidney injury.

	sCr (≤48 h)	Urinary output	Miscellaneous criteria
AKIN class I	(a) sCr increase ≥1.5-fold (b) sCr increase ≥0.3 mg/dL	Urine < 0.5 mL/kg/h for 6 h	
AKIN class II	sCr increase ≥2-fold	Urine < 0.5 mL/kg/h for 12 h	
AKIN class III	(a) sCr increase ≥3-fold (b) sCr acute rise ≥0.5 mg/dL if baseline sCr ≥4 mg/dL	(a) Urine < 0.3 mL/kg/h for 24 h (b) Anuria for 12 h	Patients who receive renal replacement therapy

AKIN = Acute Kidney Injury Network; sCr = serum creatinine (mg/dL).

Table 3
Available biomarkers in acute kidney injury.

	Serum	Urine
Cystatin C	(+)	(+)
Neutrophil gelatinase-associated lipocalin (NGAL)	(+)	(+)
L-type fatty acid binding protein (L-FABP)	(+)	(+)
Interleukin-18 (IL-18)	(+)	(+)
Kidney injury molecule-1 (KIM-1)	(−)	(+)
Netrin-1	(−)	(+)
N-acetyl-β-D-glucosaminidase (NAG)	(−)	(+)
α1-macroglobulin (α1-MG)	(−)	(+)

treatment plan.[76] Advanced care planning could help identify patient preferences.[77] A time-limited trial of dialysis might be another choice.[78] Prognostic models for elderly patients with AKI are not yet available, so decisions on whether to initiate or discontinue RRT are still made on an individual basis.

8. Courses and outcomes of AKI in the elderly

8.1. Mortality after AKI in the elderly

Elderly patients suffering from AKI have a high short-term mortality (20–45%)[11,41,45] that varies based on whether the AKI is hospital acquired (higher mortality) or community acquired (lower mortality).[79] An intrinsic origin of AKI also carries a worse prognosis than prerenal or postrenal origins for AKI.[79] The overall outcomes have improved in recent years despite an increase in concomitant comorbidities.[80] The short-term mortality associated with AKI in the elderly has continued to decline along with the mortality for the entire AKI population.[45]

Long-term mortality rates are also elevated in patients with AKI, and patient age plays a significant role.[57] Patients with AKI have 90-day, 6-month, 1-year, and 5-year survival rates ranging 46–74%, 55–73%, 57–65%, and 65–70%, respectively.[81] Elderly patients with AKI have even higher long-term mortality rates than their younger counterparts, but the degrees of elevated risk vary.[49,82] One report found no significant differences in the risk of death between dialysis-requiring patients with AKI after cardiac surgery who were ≥70 years of age, or <70 years.[83] The effect of AKI on long-term survival might be mitigated by the emergence of other comorbidities, therefore deviating the results.[13] The synergistic effects of disease combinations represent a significant confounder of study interpretations.[79]

8.2. CKD and end-stage renal disease after AKI in the elderly

AKI is no longer considered a completely reversible condition, and development of CKD and end-stage renal disease are often reported. Diagnosis of AKI during admission is associated with 3–20-fold higher risk of subsequent CKD in the ensuing months to years.[84–86] Furthermore, AKI after renal transplantation can exacerbate the risk of graft failure.[56] A recent meta-analysis also highlighted the fact that patients >65 years in whom AKI has been diagnosed have a significantly higher chance of nonrecovery of renal function than younger patients (relative risk 1.28; $p < 0.01$).[46] However, interpretation of these studies should be conducted with the understanding that mortality from AKI is an important competing risk during the analyses. Results are also often confounded by definitions of CKD.[13,84] Mechanisms explaining higher risks for CKD after AKI can be deducted from experimental models and include diminished tubular epithelial cell proliferative potentials, lower rates of cellular turnover, reduced growth factor expression, and less capability to recruit progenitor cells to injury sites for repair.[48,87]

8.3. Functional outcomes after AKI in the elderly

The quality of life (QoL) after AKI is rarely investigated in the literature, and none of the available studies discuss the elderly. One small-scale study suggested that AKI survivors have lower physical health summary scores but similar mental health scores compared with the general population [based on the 36-Item Short Form Health Survey (SF-36)].[88] Another small study suggested no significant decrease in QoL after 3 years of follow-up in dialysis-requiring AKI survivors [based on the Medical Outcomes Study (MOS-SF20) questionnaires].[89] Ahlström et al[90] identified lower overall health-related QoL in dialysis-requiring AKI survivors at 2.4 years of follow-up. Another Finnish nationwide survey also reached similar results (based on the EuroQoL instruments).[91] However, it is interesting to observe that these survivors perceived their health to be as good as that of patients not requiring dialysis post-AKI.

In conclusion, the percentage of elderly individuals continues to increase and this population consumes increasingly more healthcare resources, often with less favorable outcomes. The elderly are more susceptible to the development of AKI due to their comorbidities, polypharmacy, and various interventions that introduce injury to their kidneys. AKI in the elderly is often detected more slowly or even masked, which increases the risk for complications and poor outcomes. The development of AKI is associated with a higher risk for mortality as well as long-term detrimental effects such as CKD or end-stage renal disease in the elderly patient. Healthcare providers must be more aware of AKI and its devastating effects on the elderly and devote more resources to reducing the incidence of AKI in this population.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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